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Remarks:
A request for correction of the description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 3.).

(54) Compositions containing polyanionic polysaccharides and hydrophobic bioabsorbable polymers

(57) Biocompatible compositions comprising polyanionic polysaccharides combined with hydrophobic bioabsorbable polymers as well as methods for making and using the compositions are described.

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bowel anastomoses, endoscopic surgical procedures, vascular grafts, and any prosthetic device requiring gluing together or sealing of potential leakage sites; as a new biocompatible fiber for processing into thread, braids, woven and non-woven webs, weaves and mats, and sutures for wound closure; sclerosing agents for varicose vein removal, tumors, and aneurisms; artificial extracellular matrix materials for cell and tissue replacement for skin, tendon, ligament, bone, cartilage, and other tissues and organs.

The time period required to effectively prevent adhesion will vary according to the type of surgery or injury involved. Generally, the tissues should remain separated for at least 48 hours, and preferably, for a period of at least 7 days. Accordingly, the rate of diffusion of the composition used in any particular situation can be varied, for example, by altering the extent of the composition's solubility or insolubility, by varying the density of the polyanionic polysaccharide used, or by varying the thickness of the film, foam, gel, or fiber used. These characteristics can be altered by routine procedures, and the properties desired for any type of surgery or trauma can be determined by routine experimentation using the guidance of the examples described herein.

Films, foams, or gels of the invention can further be used for drug delivery. For example, in the case where rapid, localized delivery is desirable, water-soluble compositions within the invention can be used. Alternatively, compositions containing water-insoluble polyanionic polysaccharides are useful for sustained release drug delivery. The drug to be delivered can be dispersed within the composition, or can be covalently bonded to the foam, film, or gel as described, for example, in R.V. Sparer et al., 1983, Chapter 6, pages 107-119, in T.J. Roseman et al., Controlled Release Delivery Systems, Marcel Dekker, Inc., New York; and the foam, film, or gel can then be implanted or injected at the locus where delivery is desired.

Claims

1. A water-insoluble biocompatible composition characterised in that it comprises a polyanionic polysaccharide combined with a hydrophobic bioabsorbable polymer and optionally a drug and/or biological cells.

2. A composition as claimed in claim 1 wherein the said polyanionic polysaccharide is in the form of a water-insoluble derivative.

3. A composition as claimed in claim 1 or claim 2 wherein the said polyanionic polysaccharide is selected from carboxymethylcellulose, carboxymethylamylose, hyaluronic acid, chondroitin-6-sulfate, heparin, heparin sulfate and dermatan sulfate, preferably carboxymethylamylose, carboxymethylcellulose or hyaluronic acid.

4. A composition as claimed in any of claims 1 to 3 wherein the said biocompatible composition comprises two or more polyanionic polysaccharides, preferably hyaluronic acid and carboxymethylcellulose.

5. A composition as claimed in any of claims 1 to 4 wherein the said hydrophobic bioabsorbable polymer is selected from polyglycolide, polylactide, polydioxanones, polyestercarbonates, polyhydroxyalkonates, polylactones and copolymers thereof, preferably polyglycolide, polylactide, a copolymer of polyglycolide/polylactide, a copolymer of polyglycolide/polycaprolactone or a copolymer of polylactide/polycaprolactone.

6. A composition as claimed in any of claims 1 to 5 wherein the said composition is in the form of a membrane, a foam or fibers.

7. A composition as claimed in any of claims 1 to 6 wherein the said drug is selected from proteins, biopolymers, steroids, non-steroidal anti-inflammatory drugs, cytotoxic agents, antibiotics and oligonucleotides, preferably a growth factor, such as TGF-β_2, which is capable of further enhancing the growth and proliferation of cells at a site of injury in a mammal, or an antibiotic.

8. A composition as claimed in any of claims 1 to 7 wherein the said composition is admixed or infiltrated with the said cells.

9. A composition as claimed in any of claims 1 to 8 wherein the said cells are derived from a mammal, preferably a human, and more preferably comprise fibroblasts, osteocytes, chondrocytes, keratinocytes, tenocytes, non-differentiated mesenchymal cells or a mixture of at least two cell types.

10. A method of making a water-insoluble biocompatible composition as claimed in any of claims 1 to 9 characterised in that it comprises combining a polyanionic polysaccharide with a hydrophobic bioabsorbable polymer under suit-

able conditions.

11. A method as claimed in claim 10 wherein the said polyanionic polysaccharide is in the form of a film or foam.

12. A method as claimed in claim 10 or claim 11 wherein the said combination is achieved by coating preferably only one side of the said polyanionic polysaccharide with the said hydrophobic bioabsorbable polymer, by spraying the said hydrophobic bioabsorbable polymer onto the said polyanionic polysaccharide, by brushing the said hydrophobic bioabsorbable polymer onto the said water-insoluble polyanionic polysaccharide derivative, by dipping the said water-insoluble polyanionic polysaccharide derivative into the said hydrophobic bioabsorbable polymer, by dispersing fibers of the said hydrophobic bioabsorbable polymer into an aqueous suspension of the said polyanionic polysaccharide or by compressing a film of the said hydrophobic bioabsorbable polymer onto the said polyanionic polysaccharide.

13. A method for promoting cell growth and proliferation characterised in that it *in vitro* comprises: obtaining a sample of the said cells; admixing the said cells with a water-insoluble biocompatible matrix which is a composition as claimed in any of claims 1 to 9; and culturing the said admixture under conditions suitable to promote growth and infiltration of the said cells into the said matrix.

14. A composition for promoting cell growth and proliferation *in vivo* at the site of an injury in a mammal characterised in that it comprises a sample of cells which are capable of facilitating healing of the said injury, admixed with a water-insoluble biocompatible matrix, which is a composition as claimed in any of claims 1 to 9.

15. A composition as claimed in claim 14 wherein the said admixture is cultured under conditions suitable to promote proliferation and infiltration of the said cells into the said matrix prior to placement at a site of injury in a mammal.